Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V:

Olaparib (new therapeutic indication: Prostate cancer, BRCA1/2-mutations, progression after hormonal treatment)

of 3 June 2021

At its session on 3 June 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of olaparib in accordance with the resolution of 16 January 2020:

Olaparib

Resolution of: 3 June 2021
Entry into force on: 3 June 2021
BAnz AT TT. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 3 November 2020):

Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior treatment that included a new hormonal agent.

Therapeutic indication of the resolution (resolution of 3 June 2021):

see new therapeutic indication according to marketing authorisation

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adult patients with metastatic castration-resistant prostate cancer (mCRPC); BRCA1/2-mutated (germline and/or somatic); progressive disease after previous treatment with abiraterone and/or enzalutamide

Appropriate comparator therapy:

Patient-individual treatment with selection of abiraterone, enzalutamide, cabazitaxel and docetaxel; taking into account previous therapies as well as the marketing authorisation of the respective medicinal product.

Extent and probability of the additional benefit of olaparib compared to the patient-individual treatment:

Hint for a considerable additional benefit.

Study results according to endpoints:[1]

Adult patients with metastatic castration-resistant prostate cancer (mCRPC); BRCA1/2-mutated (germline and/or somatic); progressive disease after previous treatment with abiraterone and/or enzalutamide

[1] Data from the dossier assessment of the IQWiG (A20-106) and from the addendum (A21-51), unless otherwise indicated.

Summary of results of relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↑	Advantages in pain (strongest pain, impairment due to pain) and symptomatic skeletal-related events (occurrence of spinal cord compression)
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↔	Disadvantages in the specific AEs (anaemia, nausea)
Explanations: ↑: statistically significant and relevant positive effect with high or unclear risk of bias ↓: statistically significant and relevant negative effect with high orunclear risk of bias ↑↑: statistically significant and relevant positive effect with low risk of bias ↓↓: statistically significant and relevant negative effect low risk of bias ↔: no relevant difference ∅: no data available n.a.: not assessable		

PROfound study:

Olaparib + androgen deprivation therapy (ADT) *vs.* abiraterone + prednisone or prednisolone + ADT *or* enzalutamide + ADT

Study design: randomised, parallel, open-label

2. data cut-off of 20/3/2020

Relevant sub-population: Patients with a BRCA1/2-mutation

Mortality

Endpoint	Olaparib + ADT		Abiraterone + P + ADT or enzalutamide + ADT		Intervention vs Control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95 % CI]; p value Absolute difference (AD)[a]
Overall survival					
	102	20.1 [17.3; 26.8] *53 (52.0)*	58	14.4 [10.7; 18.9] *41 (70.7)*	0.60 [0.40; 0.91]; 0,0117 AD: 5.7 months

Morbidity

Endpoint	Olaparib + ADT		Abiraterone + P + ADT or enzalutamide + ADT		Intervention vs Control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95 % CI]; p value Absolute difference (AD)[a]
Progression-free survival (PFS)					
radiological progression-free survival (rPFS)	102	9.8 [7.6; 11.3] *62 (60.8)*	58	3.0 [1.8; 3.5] *51 (87.9)*	0.19 [0.12; 0.29]; < 0.0001 AD: 6.8 months
Symptomatology					
Pain (BPI-SF)					
worst pain (BPI-SF items 3)	102	22.8 [14.5; n. a.] *25 (24.5)*	58	5.5 [2.6; n. a.] *19 (32.8)*	0.35 [0.18; 0.67]; < 0.001
Pain intensity (BPI-SF items 3-6; shown as supplementary)	102	n.a. *19 (18.6)*	58	5.5 [3.6; n. a.] *15 (25.9)*	0.33 [0.15; 0.69]; 0.002

Endpoint	Olaparib + ADT			Abiraterone + P + ADT or enzalutamide + ADT			Intervention vs Control
	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	Mean difference [95% CI] p value Hedges' g:
Pain (BPI-SF)							
Impairment due to pain (BPI-SF items 9a-g)	76	1.68 (2.18)	-0.05 (0.12)	45	1.79 (2.15)	1.13 (0.24)	-1.18 [-1.72; -0.65]; < 0.001 Hedges' g: -0.91 [-1.30; -0.52]

Endpoint	Olaparib + ADT		Abiraterone + P + ADT or enzalutamide + ADT		Intervention vs Control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95 % CI]; p value Absolute difference (AD)[a]
Symptomatic skeletal-related events					
symptomatic skeletal related events	102	n.a. *18 (17.6)*	58	n.a. *12 (20.7)*	0.64 [0.31; 1.39]; 0.255
Endpoint Components:					
new symptomatic, pathological bone fractures	102	n.a. *5 (4.9)*	58	n.a. *4 (6.9)*	0.56 [0.15; 2.31]; 0.310
Radiotherapy to prevent or alleviate skeletal symptoms	102	n.a. *15 (14.7)*	58	n.a. *8 (13.8)*	0.88 [0.38; 2.20]; 0.862
Occurrence of spinal cord compression	102	n.a. *4 (3.9)*	58	n.a. *7 (12.1)*	0.28 [0.07; 0.92]; 0.026
orthopaedic surgery because of bone metastases	102	n.a. *1 (1.0)*	58	n.a. *2 (3.4)*	0.22 [0.01; 2.29]; 0.207

Endpoint	Olaparib + ADT			Abiraterone + P + ADT or enzalutamide + ADT			Intervention vs Control
	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	Mean difference [95% CI] p value Hedges' g:
Health status (EQ-5D VAS)							
	No usable evaluations.						

Health-related quality of life

Endpoint	Olaparib + ADT	Abiraterone + P + ADT or enzalutamide + ADT	Intervention vs Control

	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	Mean difference [95% CI] p value Hedges' g:
FACT-P							
	No usable evaluations.						

Side effects

Endpoint	**Olaparib + ADT**		**Abiraterone + P + ADT or enzalutamide + ADT**		Intervention vs Control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95 % CI]; p value Absolute difference (AD)[a]
Adverse events (presented additionally)					
	102	0.5 [0.4; 0.9] *99 (97.1)*	58	0.9 [0.7; 1.0] *52 (89.7)*	-
Serious adverse events (SAE)					
	102	n.a. *38 (37.3)*	58	11.1 [6.7; n. a.] *14 (24.1)*	0.99 [0.53; 1.93]; 0.999
Severe adverse events (CTCAE grade 3 or 4)					
	102	8.3 [5.7; n. a.] *56 (54.9)*	58	12.7 [3.4; n. a.] *23 (39.7)*	0.97 [0.60; 1.63]; 0.887
Therapy discontinuation because of adverse events					
	102	n.a. *19 (18.6)*	58	n.a. *6 (10.3)*	1.15 [0.47; 3.23]; 0.689
PRO-CTCAE					
	No usable evaluations.				
Specific adverse events					
MDS (PT, AE)					
	102	n. d.	58	n. d.	n. d.
AML (PT, AE)					
	102	n. d.	58	n. d.	n. d.
Pneumonitis (PT, AE)					
	102	n. d.	58	n. d.	n. d.
Anaemia (PT, severe AEs)					

	102	n.a. *24 (23.5)*	58	n.a. *1 (1.7)*	11.60 [2.42; 208.02]; 0,003
Nausea (PT, AE)					
	102	14.8 [3.6; n. a.] *47 (46.1)*	58	n.a. *10 (17.2)*	2.79 [1.46; 5.90]; 0.003

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.

Abbreviations used:
AD: Absolute difference: ADT: Androgen deprivation therapy; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory - Short Form; BRCA: Breast cancer susceptibility gene; CTCAE: Common Terminology Criteria for Adverse Events; EPAR: European public Assessment Report; HR: hazard ratio; n. d.: no data; CI: Confidence interval; n: number of patients with (at least 1) event; MDS: myelodysplastic syndrome; N: number of patients evaluated; n. c. = not calculable; n.a. = not achieved; P: Prednisone/Prednisolone; PRO: Patient-reported outcome; PT: preferred term; RCT: randomised controlled trial; SAE: serious adverse event; AE: adverse event; vs: versus

2. Number of patients or demarcation of patient groups eligible for treatment

Adult patients with metastatic castration-resistant prostate cancer (mCRPC); BRCA1/2-mutated (germline and/or somatic); progressive disease after previous treatment with abiraterone and/or enzalutamide

approx. 1490 to 1980 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Lynparza (active ingredient: olaparib) at the following publicly accessible link (last access: 17 March 2021):

https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_de.pdf

Treatment with olaparib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with prostate cancer.

Medicinal castration with a GnRH agonist or antagonist should be continued during the treatment of patients who have not been surgically castrated.

Prior to initiation of therapy with Lynparza, patients with BRCA1/2-mutated metastatic castration-resistant prostate cancer must have evidence of a deleterious or suspected deleterious BRCA1/2-mutation. BRCA1/2-mutation status should be detected by an experienced laboratory using a validated test method. Patients who test positive for mutation of the BRCA1/2 genes should be offered genetic counselling according to national regulations.

4. Treatment costs

Annual treatment costs:

Adult patients with metastatic castration-resistant prostate cancer (mCRPC); BRCA1/2-mutated (germline and/or somatic); progressive disease after previous treatment with abiraterone and/or enzalutamide

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Olaparib	€ 69,059,30
LHRH analogue	€ 1,781.48 - € 2,154.36
Total	€ 70,840.78 - € 71,213.66
Appropriate comparator therapy:	
Abiraterone acetate + prednisone or prednisolone + LHRH analogue	
Abiraterone acetate	€ 45,842,70
Prednisone or prednisolone	€ 55.70 - € 67.20
LHRH analogue	€ 1,781.48 - € 2,154.36
Total	€ 47,679.88 - € 48,064.26
Enzalutamide + LHRH analogue	
Enzalutamide	€ 45,028,23
LHRH analogue	€ 1,781.48 - € 2,154.36
Total	€ 46,809.71 - € 47,182.59
Cabazitaxel + prednisone or prednisolone	
Cabazitaxel	€ 59,154,95
Prednisone or prednisolone	€ 55.70 - € 67.20
Total	€ 59,210.65 - € 59,222.15
Docetaxel + prednisone or prednisolone	
Docetaxel	€ 21,230,61
Prednisone or prednisolone	€ 104.17 - € 95.34

Name of therapy	Annual treatment costs/patient
Total	€ 21,334.78 - € 21,325.95

Cost after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 May 2021).

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 3 June 2021.

The justification to this resolution will be published on the G-BA website at www.g-ba.de.

Berlin, 3 June 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken